Pergamon

Tetrahedron: Asymmetry, Vol. 8, No. 23, pp. 3955–3975, 1997

Printed in Great Britain

PII: S0957-4166(97)00599-5

0957-4166/97 $17.00 + 0.00

Rotational features of carbon–nitrogen bonds in axially chiral *o*-*tert*-butyl anilides and related molecules. Potential substrates for the 'prochiral auxiliary' approach to asymmetric synthesis †

Dennis P. Curran *,[a,*] Gregory R. Hale,[a] Steven J. Geib,[a] Aaron Balog,[a] Quezia B. Cass *,[b] Ana Luiza G. Degani,[b] Marcelo Z. Hernandes [b] and Luiz Carlos G. Freitas [b]

[a] Department of Chemistry, University of Pittsburgh, Pittsburgh, PA 15260, USA

[b] Depto. de Química, Universidade Federal de São Carlos, Cx. Postal 676, São Carlos 13565-905, SP, Brazil

Abstract: A new strategy for asymmetric induction termed the 'prochiral auxiliary' approach is introduced. Reactions of acylating agents with prochiral *N*-methyl-*o*-*tert*-butyl aniline provide anilides that are axially chiral by virtue of restricted rotation about the N–Ar bond. Rotamer populations about the amide bond (E/Z) were studied by ^{1}H NMR. Several pairs of enantiomeric *o*-*tert*-butyl anilides were separated by chiral chromatography and barriers about the N–Ar bond were measured by thermal racemization. Related *o*-(1-(trialkylsilyloxy)-1-methylethyl) anilides were also studied. © 1997 Published by Elsevier Science Ltd. All rights reserved.

Introduction

The conversion of an achiral molecule to a chiral one with concomitant bond formation is often accomplished by using either a chiral auxiliary or a chiral catalyst.[1] A representative example of each process as applied to a Diels–Alder reaction is shown in Figure 1. The chiral auxiliary approach is exemplified by an Evans isoxazolidinone.[1] A chiral auxiliary is attached to a substrate molecule, used to direct a stereoselective bond forming reaction, and then removed and (ideally) recovered for reuse. Although not required in principle, the complementary chiral catalytic approach often benefits from the introduction of an 'achiral auxiliary' to form a suitable complex with the chiral catalyst and to direct the subsequent bond forming reaction (Figure 1). After completion of the process, the achiral auxiliary is removed and recycled for reuse.

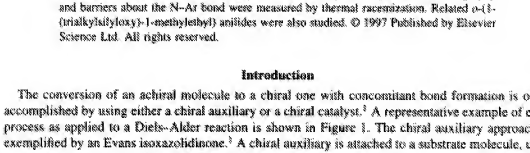


Figure 1. The 'chiral auxiliary' and 'chiral catalyst' approaches.

† Dedicated to Professor Herbert C. Brown on the occasion of his 85th birthday.

* Corresponding author. Email: curran+@pitt.edu

The merits and demerits of chiral auxiliaries and chiral catalysts have been widely discussed.[1] The catalysis approach is frequently and justifiably promoted for its efficiency. The auxiliary approach requires stoichiometric amounts of a chiral source, but in reactions that are not completely selective, it produces mixtures of diastereomers. Since these are often easier to separate than enantiomers, it can be easier to obtain enantiomerically pure products. Furthermore, the chiral auxiliary approach tends to have more generality across different types of reactions. This is because auxiliaries are covalently bonded to substrates and can be used across a range of reaction types, whereas catalysts must often be tailored to the reaction that they are promoting. Nonetheless, a number of privileged ligand structures,[1] such as BINAP/BINOL[2] and TADDOL,[3] have proven useful for making a diverse assortment of asymmetric catalysts.

There is a hybrid approach to generation of asymmetry that — at least in principle — combines the advantages of both the chiral catalyst approach and the chiral auxiliary approach. We call this the 'prochiral auxiliary approach', and it is summarized in Figure 2. The approach requires the combination of a substrate and a prochiral auxiliary to form a chiral adduct. For this to occur, a new element of asymmetry must be generated by the attachment. This chiral adduct is formed in a non-racemic fashion through the aid of a chiral catalyst. The resulting chiral substrate can then be used in assorted reactions to form bonds in a stereocontrolled fashion. In the end, the prochiral auxiliary is removed to give one enantiomer of the chiral product.

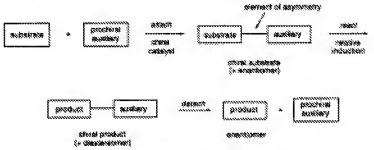


Figure 2. The 'prochiral auxiliary' approach.

The standard chiral catalyst approach combines two achiral molecules to make a third one, and then uses the chiral catalyst to induce the desired transformation. The prochiral auxiliary approach combines the two achiral molecules with a chiral catalyst to make a third chiral molecule. This molecule can now effectively be used as in the chiral auxiliary approach; it is amenable to a wide assortment of subsequent bond forming reactions, which occur by relative (not absolute) asymmetric induction to provide diastereomeric (not enantiomeric) products. The initial generation of asymmetry traces back to a chiral catalyst, so the process effectively shares the best features of both the chiral catalyst and chiral auxiliary approaches. On the down side, the initial products from the catalytic reaction are enantiomers, so the catalyst must either provide very high ee or there must be an easy physical method to enrich the products. Nonetheless, once this goal is accomplished, the resulting product can be used for a wide assortment of reactions. Effectively, the asymmetry of a single catalyst is relayed across a diverse assortment of transformations which, in the standard chiral catalysis approach, would each require their own special catalyst. Furthermore, because the auxiliary is prochiral rather that chiral, it can be reused after cleavage to make either enantiomer of the product by choosing the appropriate enantiomer of the catalyst. In effect, there is only one auxiliary in the prochiral approach, whereas the standard chiral auxiliary approach requires two (enantiomeric) auxiliaries.

The prochiral auxiliary approach is closely related to a classical strategy for asymmetric synthesis in which two prochiral molecules are combined without any chiral influence.[4] The resulting racemic chiral substrate is resolved and then the process continues as in Figure 2.

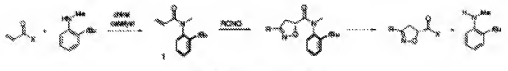


Figure 3. Axially chiral anilides in the prochiral auxiliary approach.

We have not yet succeeded in fully reducing to practice the strategy in Figure 2. Figure 3 shows an approach currently being developed in our labs. In this approach, an achiral acylating agent and an aniline derivative bearing a large *ortho*-substituent are combined. Such anilines are prochiral with respect to acylations; the two faces of the aromatic ring are enantiotopic. The result is an axially chiral anilide **1**, which is racemic in the absence of a catalyst, but from which we ultimately plan to prepare enantiomerically pure compounds by using a chiral catalyst. Like binaphthyl derivatives,[2-5] anilide **1** is axially chiral by virtue of slow rotation about an sp^2–sp^2 bond (N–Ar). Unlike binaphthyl derivatives,[2-5] this is a carbon–nitrogen, not a carbon–carbon bond. We[6] and more recently others[7,8] have shown that these types of amides have excellent potential for relative stereocontrol in representative types of bond forming reactions. Figure 3 shows an example of a nitrile oxide cycloaddition. Ultimately, a mild method must be available for removal of the achiral auxiliary.

None of the required transformations in Figure 3 is well precedented. We decided to focus initial efforts on the study of the features and reactions of the axially chiral amide **1**. We have already reported our preliminary results on some of the asymmetric bond forming reactions of species like **1**,[6] and we have described methods to resolve these types of enantiomers by chiral chromatography.[9] Kinetic[7a] and chemical[7b] resolutions have also recently been described. Herein we describe studies on the rotational features of these amides with respect to both the amide N–C=O bond (which generates amide E/Z isomers on rotation) and the N–C(Ar) bond (which generates enantiomers on rotation). A detailed understanding of these features is of fundamental structural interest and is needed for projected applications of *o-tert*-butyl anilides and related molecules in asymmetric synthesis. We also describe the replacement of the *tert*-butyl group with a 1-silyloxy-1-methylethyl group ($R_3SiO(Me_2)C$–), and the effect of this replacement on bond rotation, stereoselection in nitrile oxide cycloadditions, and cleavage properties.

Results and discussion

Amide N–CO bond rotamers

N,N-Disubstituted amides generally prefer to exist as the Z-rotamer (Figure 4) presumably for steric reasons.[10] However, it has been known for over 30 years that *N*-methylacetanilides prefer the E-rotamer,[11,12] which has the phenyl group and the amide oxygen trans-disposed. This seemingly counterintuitive preference can be rationalized by the twisting of the *N*-phenyl group, as shown in Figure 4.[13,14] This twist, which forms the basis for separations of enantiomeric atropisomers described below, makes the phenyl group effectively smaller and may cause electron–electron repulsion between the lone pairs on oxygen and the π-system of the aromatic ring.[12c]

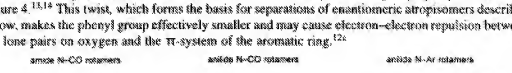
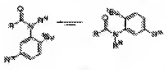


Figure 4. Rotational features of amides and anilides.

Rotation of the amide N–CO bond from E to Z or back does not racemize an axially chiral amide. But

Table 1. E/Z Rotamer ratios of *o*-*tert*-butyl-*N*-alkyl acetanilides



2 E (racemic) 2 Z

Entry	R	R^N	R^m	$CDCl_3$ (2E/Z)	CD_3SOCD_3 (2E/Z)
a	CH_2=CH	Me	H	~60/1	16/1
b	^{E}CH_3CH=CH	Me	H	~60/1	20/1
b[m]	^{E}CH_3CH=CH	Me	^{t}Bu	~60/1	—
c	^{E}PhCH=CH	Me	H	>60/1	—
c[m]	^{E}PhCH=CH	Me	^{t}Bu	>60/1	—
d	^{E}(p-Br)PhCH=CH	Me	H	>60/1	—
e	CH_2=C(CH_3)	Me	H	1.5/1	1/1.3
e[m]	CH_2=C(CH_3)	Me	^{t}Bu	2.7/1	1.2/1
f[m]	^{E}CH_3CH=C(CH_3)	Me	^{t}Bu	2.3/1	1/1
g[m]	^{E}PhCH=C(CH_3)	Me	^{t}Bu	3.0/1	1.3/1
h	Ph	Me	H	2.2/1	—
i	CH_2=C(CH_3)	Et	H	2.5/1	—
j	CH_2=C(CH_3)	c-C_6H_{11}	H	10/1	—
k	Me	Me	H	22/1	—
k[m]	Me	Me	^{t}Bu	37/1	—
l	Et	Me	H	15/1	—
m	c-C_6H_{11}	Me	H	18/1	—
n[m]	^{t}Bu	Me	^{t}Bu	9/1	—

from the standpoint of asymmetric induction, the rotamer ratio in the *o*-*tert*-butyl series (R^m=*tert*-butyl) is crucial because the Z and E rotamers locate the shielding *tert*-butyl group on opposite faces of the molecule. Thus, substrates with poor rotamer ratios are liable to show poor stereoselectivities. Indeed, poor selectivities in some alkylation reactions have been tentatively attributed to this problem.[5c,7a] We therefore undertook a study of representative *N*-alkylacetanilides to garner information about substituent and solvent effects on rotamer populations.

We have previously communicated that the Z rotamer is highly favored in simple *N*-methyl acrylamide derivatives **2a** (Table 1).[6a] Although the ^{1}H NMR spectrum of this compound in $CDCl_3$ appears to be that of a single pure compound, there was consistently a very small singlet in the N–Me region (3.36 ppm) adjacent to the large singlet for the N–Me group in **2a** (3.24 ppm). Several lines of evidence led us to conclude that this small peak was the N–Me signal of the E rotamer. First, the integrated ratio of the two singlets was consistently about 60/1, despite assorted methods for purification. Second, the ratio of the two peaks was solvent dependent (see below). Third, a number of related compounds provided similar pairs of small and large peaks in differing ratios (see below). And finally, on warming, the spectrum appeared to pass through a coalescence where the larger peak broadened and resharpened and the smaller peak disappeared. We thus conclude that the rotamer ratio of **2a** in chloroform is about 60/1 in favor of the E-rotamer.

The spectra of a series of related amides were recorded in $CDCl_3$ (and sometimes in DMSO-d_6), and the rotamer ratios listed in Table 1 were obtained by integration of the appropriate resonances (typically the N–Me singlets). These amides fall into two classes: those which bear *meta*'-*tert*-butyl groups (denoted with a superscript 'm') and those which do not. In general, downfield N–Me singlets were assigned to the Z-rotamers and upfield singlets to the E-rotamers.[10a] The data in Table 1 reveal some interesting trends. Like the unsubstituted derivative **2a**, acrylates bearing substituents on the β-vinyl carbon (**2b–d**) showed a large preference for the E-rotamer. However, the methacryloyl and tigloyl derivatives **2e** and **2f** and the benzoyl derivative **2h** exhibited very modest preferences (3/1)

Table 2. Solvent effect on E/Z ratios

Solvent	2b E/Z	2e E/Z
C_6D_6	>60/1	1.8/1
$CDCl_3$	>60/1	1.5/1
CD_2Cl_2	36/1	1/1.2
CD_3COCD_3	30/1	1/1
CD_3OD	27/1	1/1.4
$(CD_3)_2NCDO$	23/1	1/1
CD_3CN	22/1	1/1.7
$CD_3S(O)CD_3$	20/1	1/1.3

for the E-rotamer. In these cases, there was obvious doubling of most or all of the peaks in the spectrum. In the alkyl series (**2k–n**), the *N*-acetyl derivative **2k** exhibited the highest E preference (22/1), while the pivaloyl derivative **2n** had only a 9/1 preference. The intermediate propanoyl **2b** and cyclohexanecarbonyl **2m** derivatives did not show a regular trend with the primary substrate exhibiting a marginally lower E-preference (15/1) than the secondary one (18/1). In the methacrylate series, increasing the size of the *N*-alkyl substituent from methyl (**2e**, 1.5/1) to ethyl (**2i**, 2.5/1) to cyclohexyl (**2j**, 10/1) reinstates the E-selectivity. In cases where both unsubstituted and *meta'*-*tert*-butyl analogs are available (**b**, **c**, **e**, **k**), the rotamer ratios are qualitatively similar, although the *meta'*-*tert*-butyl derivatives may have a somewhat higher preference for the E-rotamer.

In DMSO-d_6, there was a uniformly reduced preference for the E-isomer. This solvent effect was studied in more detail for the crotonate **2b** and methacrylate **2e** derivatives, and the rotamer ratios in eight different solvents are reported in Table 2. For the crotonate derivatives, the E-preference drops from >60/1 to as low as 20/1. The crotonate exhibits low E-preferences in the less polar solvents, but has no preference or a low Z-preference in more polar solvents.

In two cases, crystal structures confirmed the rotamer assignments and provided additional information. The crystal structure of the racemic cinnamoyl derivative **2c** is shown in Figure 5. As expected, this compound exists in the E-rotamer. The amide is planar, and is completely conjugated with the acryloyl group, which lies in the expected[15] s-*cis* disposition. The plane of the anilide aromatic ring is roughly perpendicular to the acrylamide plane, and the *tert*-butyl group is disordered (only one orientation shown), which is indicative of rapid rotation of this group in the crystal. The *tert*-butyl group appears well positioned to shield one face of the acryloyl group of this molecule.

Figure 5. Crystal structure of **2c**.

The crystal structure of the methacryloyl derivative **2e** was fascinating. Though the E-rotamer is slightly favored in $CHCl_3$, crystals deposited from this solvent possessed a Z-conformation, as shown in Figure 6.[16] The planes of the aryl group and the amide are again roughly perpendicular, and the methacryloyl group is not in the plane of the amide, but is instead also roughly perpendicular. This twisting is anticipated by prior crystal studies.[11b,17] Clearly, the *N*-*tert*-butyl group in **2c** is not well positioned to block a face of the alkene.[18]

Dissolution of a crystal of **2e** in $CDCl_3$ at −60°C provided a spectrum of the nearly pure minor rotamer from the mixture, thereby confirming the rotamer assignment. On gradual warming, we

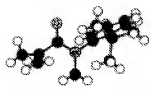


Figure 6. Crystal structure of **2e**.

first noticed equilibrium to the E-isomer at about −35°C, and we estimate that the half-life at this temperature is about 1 h.

All of this information is reasonably consistent with the picture in Figure 4 in which the normal preferences for amides are superimposed on the special needs of *N*-alkylanilides. The addition of the *tert*-butyl group appears to decrease the E-preference, consistent with its increased size. For example, Itai reports a 15/1 ratio of E/Z rotamers for *N*-2-dimethylbenzanilide,[10b] but the *tert*-butyl derivative **2h** exhibits a 2.2/1 ratio. Likewise, increasing the size of the acyl group favors the Z-rotamer while increasing the size of the *N*-alkyl group favors the E-rotamer. The methacryloyl and benzoyl derivatives behave as especially large groups because of their twisting. Intuitively, one expects that the Z-rotamer has the larger dipole moment, and this is supported by the solvent studies.

From the standpoint of asymmetric induction, the acrylates and the methacrylates are the most important. These molecules are directly used in things like cycloaddition and conjugate addition reactions, and they also model other sp^2 intermediates like enolates and radicals. The acrylates have a high E/Z ratio and prefer the *s-cis* conformation; this bodes well for their reactions as well as for the reactions of Z-enolates and radicals. But the methacrylates are twisted and exist as E/Z rotamer mixtures, suggesting that their reactions (and those of related disubstituted enolates and radicals) may be more difficult to conduct with high selectivity.[19]

Amide N–Ar bond rotamers

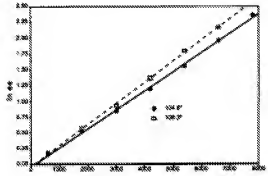
Enantiomeric atropisomers result from the twisting on the N–Ar bond of these anilides, and this feature is central to the achiral auxiliary strategy. We deduced from related anilides bearing two *ortho*-groups (which have very high barriers to rotation[13]) that compounds bearing a single but large *ortho* group would resist racemization as well. To confirm and quantify this deduction, we have resolved a number of amides and measured racemization barriers. In addition, we have tested the ability using MOPAC calculations to reproduce the experimental barriers.

Amides were resolved by semi-preparative or preparative HPLC by using a variant of the analytical method that we reported previously.[9] Satisfactory separations were achieved for six different amides either on an amylose tris[(*S*)-1-phenylethylcarbamate] coated onto APS-Hypersil (120 Å, 5 μm, 15% w/w) semi-preparative column or on a cellulose tris(3,5-dimethylphenylcarbamate) coated onto APS-Hypersil (120 Å, 5 μm, 20% w/w) preparative column. A representative chromatogram for the separation of 10.4 mg of crotonanilide **2b**^{m} is shown in Figure 7. Scales of semi-preparative runs ranged from 5 to 15 mg, while 80 mg of benzanilide **2h**^{m} was separated with good purity of both enantiomers on a preparative column.

The racemization data for six amides are summarized in Table 3. Pairs of enantiomers were thermally racemized and their barriers were determined by following the process by analytical HPLC using a column of amylose tris[(*S*)-1-phenylethylcarbamate] coated onto APS-Nucleosil (500 Å, 7 μm, 20% w/w). Five of the amides have m′-^{t}Bu groups, and these extra *tert*-butyl groups proved to be inconsequential in racemization and stereoselective reactions. Representative data for racemization of both enantiomers of crotonanilide **2b**^{m} (one at 106.4°C and the other at 104.6°C) are plotted in Figure 7. Similar first-order plots were obtained for the other amides. These plots yield first order rate constants, and racemization barriers were calculated from the Eyring equation.

Efforts to confidently assign absolute configuration to these amides have not yet succeeded. Very

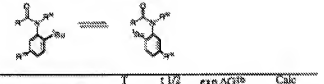
Separation of 10.4 mg of amide **2b**^{m}; amylose tris[(S)-phenylethylcarbamate], mobile phase: hexane/2-propanol (98:02 v/v); flow: 1.0 mL/min.; λ = 300 nm



Racemization was conducted in 2-butanol at 106.3° C (1st enantiomer) or 104.6° (2nd enantiomer).

Figure 7. Semi-preparative resolution of **2b**^{m} (left) and racemization (right).

Table 3. Data for amide N–Ar bond rotation[a]



Entry	Amide	R	R^N	R^M	T (°C)[a]	t 1/2 (min.)	exp $\Delta G^{\ddagger}$[b] (kcal/mol)	Calc $\Delta G^{\ddagger}$[c]
1	**2b**^{m}	^{E}MeCH=CH	CH_3	^{t}Bu	106.3 104.6	35 38	28.9 28.9	23.2/24.4
2	**2o**^{m}	^{E}MeCH=CH	C_5H_{11}	^{t}Bu	105.3 106.0	73 60	29.4 29.3	23.2/25.9
3	**2h**^{m}	Ph	CH_3	^{t}Bu	72.3 72.4	58 41	26.3 26.4	20.7/23.8
4	**2i**	C_2H_5	CH_3	H	106.0 105.5	41 44	29.0 29.1	24.3/26.9
5	**2i**^{m}	C_2H_5	CH_3	^{t}Bu	107.2 106.5	84 83	29.6 29.6	24.4/26.2
6	**2m**^{m}	c-C_6H_{11}	CH_3	^{t}Bu	96.0 90.6	96 154	28.9 28.7	24.6/28.0

a) most barriers were determined in duplicate, once with each enantiomer. The solvent was 2-butanol; b) the experimentally measured activation energies; c) calculated activation energies by using the MOPAC dihedral angle driver (see text). The first value is for rotation of the *tert*-butyl group past the *N*-alkyl group and the second for rotation past the *N*-acyl group.

recently, Kitagawa and coworkers have assigned the absolute configuration of an *N*-allyl *ortho-tert*-butyl acrylanilide.[7b] With the goal of correlating our compounds by the sign of rotation, we repeated the analytical separations in Table 2 with a polarimetric detector and learned that the levorotatory enantiomer emerges first for amides **2o**^{m}, **2i** and **2i**^{m}, and the dextrorotatory enantiomer emerges first for amides **2b**^{m}, **2h** and **2m**^{m}.

Also shown in Table 3 (last column) are a set of calculated barriers that were obtained using the AM1 Hamiltonian implemented in the MOPAC package.[19] The dihedral angle driver was used to twist the N–Ar bonds over 360° in steps of 5° and then each conformation so generated was minimized without permitting the N–Ar bond angle to rotate. All calculations were performed for isolated molecules and solvent effects were not included. The maximum energy species obtained by this method is not a transition structure, but the plot nonetheless provides an idea of the bond rotation profile.

The rotation energy profile for amide **2i** is typical, and is shown in Figure 8. Also shown are the calculated minimum energy structure and the structure of both the lower and higher of the two maxima.

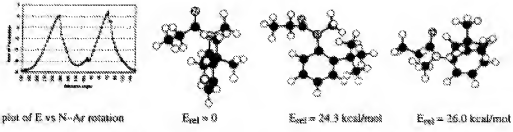


Figure 8. MOPAC bond rotation profile of **2t** along with calculated minimum and maximum energy structures.

The calculated minimum structure is similar to that expected from the X-ray crystal structure of the related molecule **2c**. As stated above, the maximum should not be considered a transition structure, but the calculations at this level repeatedly suggested that the lower energy rotation is when the *tert*-butyl group passes the N–R group rather than the N–CO group. The severe distortion of the amide N–CO bonds in the high energy structures also suggest that the rotations of the N–Ar and N–CO bonds may be coupled.

These results provide some interesting information. The measured rotation barriers for all of the *o*-*tert*-butyl anilides save one (the benzanilide **2h**$^{m'}$) fall in a rather narrow range in the vicinity of 29 kcal/mol. The calculations also provide barriers in a narrow range that is about 5 kcal/mol below the measured barriers. The benzanilide derivative has a significantly lower (but still substantial) barrier to racemization (25.9 kcal/mol); this lower barrier was predicted by the calculations. These trends seem reasonable if, as the calculations suggest, the rotation occurs by passing of the *tert*-butyl group and the *N*-alkyl group possibly in a coupled process with amide bond rotation. However, this conclusion is tentative and additional experiments and calculations are warranted. Interpretations aside, the absolute magnitude of the experimental barrier is considerable; racemization of these amides will occur with half-lives in the order of 1 year at room temperature. However, as the temperature is raised towards 100°C, the half-lives begin to decrease into the realm of reaction times (hours). Above about 120°C, racemizations are expected to be rapid (minutes or less).

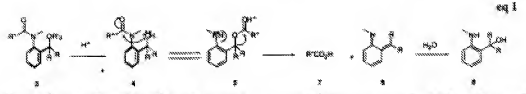
In our earlier work,[7] we focused on using *o*,*m*′-di-*tert*-butyl anilides (numbers bear superscript 'm') because they are easily synthesized. But more recently *o*-*tert*-butylaniline has become commercially available, and we have switched to this series. We hypothesized the *o*-*tert*-butyl group was the key structural element controlling rotational barriers and stereoselectivity and the *m*′-*tert*-butyl group was incidental. We have already shown that the *m*′-*tert*-butyl group does not alter stereoselectivities,[4a] and the data in Table 3 show that it has no measurable effect on the rotational barriers (compare entries 4 and 5).

Cleavable achiral auxiliaries-o-(1-silyloxy-1-methylethyl)anilides

Although the *o*-*tert*-butylanilides have high barriers to racemization and show good stereoselection in preliminary reactions, they probably lack one key feature for practical applications: ease of cleavage. We have initially addressed this problem by replacing one of the methyl groups on the *tert*-butyl group by a trialkylsilyloxy group. In preliminary experiments, the resulting *o*-(1-silyloxy-1-methylethyl)amides **3** do exhibit the feature of cleavage under mild conditions, but unfortunately, the rotation barriers of these molecules are lowered into a range that compromises their usefulness.

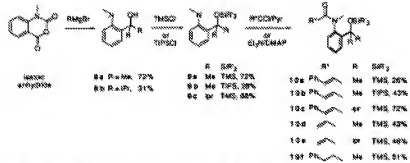
The idea underlying the design of these molecules is shown in eq 1. Upon removal of the silyl group from **3**, an equilibrium between amide **4** and ester **5** can be set up by transacylation.[36] Ester **5** may be susceptible to standard hydrolysis, but the same net result could also be accomplished by elimination to form an *o*-quinone imine **6** and acid **7**, as suggested in eq 1. Hydration of **6** should give **8**.

eq 1



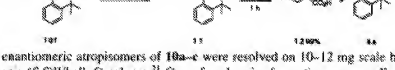
The synthesis of several members of this class of compounds is shown in eq 2. Addition of MeMgBr to isatoic anhydride provided the tertiary alcohol **8a** in 72% yield after purification by acid/base extraction. This was silylated with TMSCl and TIPSCl (triisopropylsilyl chloride), and the resulting ethers **9a** and **b** were acylated with acryloyl chloride and cinnamoyl chloride to provide the anilides **10a, b** and **d**. Silylether **9a** was also acylated with dihydrocinnamoyl chloride to give **10f**, which was used in preliminary cleavage trials. The bis-isopropyl derivative **8b** was also prepared by a similar route and converted through **9c** to **10c** and **e** in the indicated yields. The NMR spectra of all of these compounds showed a single set of resonances, suggesting that they exist largely in the E-rotamer, as expected.

eq 2



In preliminary cleavage experiments (eq 3), it was found that brief (30 min) exposure of **10f** to TBAF (tetrabutylammonium fluoride) in THF (generates **11**), followed by addition of 1 N HCl and workup after an additional hour provided a nearly quantitative yield of the cleavage products **12** and **8a**. Subsequently, we learned that the TBAF cleavage is unnecessary; direct treatment of **10f** with 1 N HCl for 1 h gives **12** in 99% yield. Under similar conditions, the related *o-tert*-butyl anilide of dihydrocinnamic acid (not shown) was recovered unchanged. Although these experiments certainly do not prove that the hypothesized mechanism (eq 1) is operating, they do suggest that this series of amides has good potential for developing mild cleavage conditions.

eq 3



The enantiomeric atropisomers of **10a–e** were resolved on 10–12 mg scale by repeated injections on a Regis (*S,S*)Whelk-O column.[21] One of each pair of enantiomers was allowed to racemize at a constant temperature, and the racemization was followed by periodic injection onto the HPLC using the same column. The data for these experiments are shown in Table 4. Unfortunately, compounds **10a** and **10b** racemized at reasonable rates even at room temperature, with half-lives of about 2 and 12 days, respectively. The barriers of 25.4 and 26.1 kcal/mol are about 3 kcal/mol lower than the corresponding *o-tert*-butyl anilides. On the other hand, the bis-isopropyl analog **10c** racemized at 60°C, and the barrier was 29.6 kcal/mol ($t_{1/2}$≈16 days). This barrier is marginally higher than that of the related *tert*-butyl analog, and it translates to a half-life of about 10 years at room temperature.

In these systems, the (silyloxy)methylethyl group behaves as if it is considerably smaller than

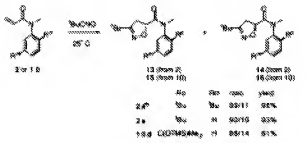
Table 4. Data for amide N–Ar bond rotations of **10a–c**

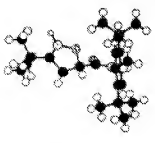
Entry	Amide	R	R^D	T (°C)	t 1/2 (hr)	exp $\Delta G^{\ddagger}$ (kcal/mol)	calc $\Delta G^{\ddagger}$ (kcal/mol)
1	**10a**	^{E}PhCH=CH	C(OTMS)Me$_2$	23	42	25.4	19.6
2	**10b**	^{E}PhCH=CH	C(OTIPS)Me$_2$	23	141	26.1	19.8
3	**10c**	^{E}PhCH=CH	C(OTMS)ipr$_2$	60	197	29.6	28.0

a *tert*-butyl group, as reflected by the decrease in the barrier to rotation. By crude comparison to some unpublished experiments,[22] it appears to provide higher rotation barriers than related isopropyl derivatives. This suggests that a gearing of the *N*-acyl (or alkyl) group between one of the methyl groups and the silyloxy group in the transition state for bond rotation is easier than the analogous gearing between two methyl groups that must take place in the *tert*-butyl systems. An effort to overcome this problem by replacing the smaller TMS group with a larger TIPS group had only a modest beneficial effect, but the change of methyl groups to isopropyl groups was effective.

To assess the effect of the silyloxy group on stereoselection, we conducted nitrile oxide cycloadditions with four racemic acrylate derivatives, and these results are summarized in eq 4. In our preliminary communication, we reported that the reaction of *t*-butyl nitrile oxide with *o,m*′-di-*tert*-butyl anilide **2a**^{m} provided atropisomeric cycloadducts **13/14** in a ratio of >97/3. In the meantime, we have isolated the minor isomer and studied the reaction more carefully, and we must now correct this report. At room temperature, the ratio of atropisomers is **13/14** about 89/11, and this increases to 93/7 at −78°C. The major isomer was crystallized, and its crystal structure is shown in eq 4. The related *o-tert*-butyl anilide **2e** provides a 90/10 ratio of products **13a/14a** at room temperature. These adducts were separated and the E/Z rotamer ratios were measured by ^{1}H NMR spectroscopy to be 13/1 and 10/1. In contrast, cycloaddition of the TMS derivative **10d** provides a 86/14 ratio of products **15d/16d**, while **10e** provides an 89/11 ratio. Equilibrium ratios of **13/14** (obtained by heating overnight at 100°C) were about 2/1. Compounds **15/16** also began to equilibrate on heating, but decomposition prevented the measurement of equilibrium values.

eq 4





Crystal structure of **13a**^{m}

Conclusions

The experiments in this paper provide a foundation for understanding the chemistry of anilides bearing large *ortho* substituents. The *o-tert*-butyl anilides exhibit several favorable features for use in the prochiral auxiliary approach including: high rotation barriers to racemization, high E/Z amide rotamer ratios in some (but not all) classes of amides, and good to excellent stereoselectivities in several

kinds of reactions. It remains to be seen whether they can be prepared through asymmetric catalysis and whether practical cleavage methods can be found. In contrast, the silyloxy-modified substrates look less promising. While they are clearly easier to cleave, the decrease in racemization barrier and the lower stereoselectivity in nitrile oxide cycloadditions do not bode well for synthetic applications.

Experimental

General

All experiments were conducted under an atmosphere of argon or nitrogen. Solvents were dried as follows: methylene chloride was distilled from CaH_2; tetrahydrofuran (THF) was distilled from sodium/benzophenone; pyridine was distilled from KOH and stored over KOH. Analytical scale HPLC separations were done on a Waters Model 590 instrument equipped with a differential refractometer. The column used was a Regis *(S,S)*Whelk-O 1 column with 5 micron packing (25 cm×4.6 mm).

Benzotriazole-1-ylmethyl-(2-tert-butylphenyl)amine

2-*t*-Butylaniline (9.57 g, 64.1 mmol) was dissolved in MeOH (100 mL) followed by addition of benztriazole (7.63 g, 64.1 mmol) and formaldehyde (37% solution in water, 6.34 mL, 64.1 mmol). The reaction was stirred for 14 h at 25°C and the white suspension was cooled to 0°C. The cooled suspension was then filtered and rinsed with cold MeOH (100 mL). The solid was dried under vacuum and used without purification.

(2-tert-Butylphenyl)methylamine

The crude triazole (15.81 g, 56.51 mmol) was dissolved in THF (300 mL) and cooled to 0°C. $NaBH_4$ (4.72 g, 124 mmol) was then slowly added in three equal portions. After 3 h, reaction was quenched slowly with H_2O (200 mL). The mixture was extracted with Et_2O (3×100 mL) and the organic layer was washed once with brine (30 mL) and dried over $MgSO_4$. Solvent evaporation gave the crude aniline which was purified by flash chromatography on silica gel eluting with hexanes:ethyl acetate (6:1) to give the pure aniline as a clear oil (75%): IR (thin film) 1497, 1441, 1296 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.29 (1H, d, *J*=8.0 Hz), 7.18 (1H, t, *J*=8.0), 6.69 (2H, m), 2.93 (3H, s), 1.44 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.74, 126.95, 125.72, 116.63, 110.87, 33.82, 30.80, 29.61; LRMS 163, 148, 133; exact mass calcd for $C_{11}H_{17}N$ 163.1361, found 163.1354.

(2-tert-Butylphenyl)ethylamine

IR (thin film) 1495, 1437, 1300 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.25 (1H, dd, *J*≈1.5, 8.0 Hz), 7.14 (1H, dt, *J*≈1.5, 8.0 Hz), 6.71 (2H, m), 3.83 (1H, bs), 3.23 (2H, q, *J*=7.2 Hz), 1.44 (9H, s), 1.34 (3H, t, *J*=7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.39, 132.70, 127.04, 125.92, 116.76, 111.68, 38.76, 33.95, 29.83, 14.89; LRMS 177, 162, 133, 106, 91, 77; exact mass calcd for $C_{12}H_{19}N$ 177.1517, found 177.1517.

(2-tert-Butylphenyl)cyclohexylamine

IR (thin film) 1501, 1441, 1304 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.26 (1H, dd, *J*=1.9, 17.4 Hz), 7.13 (1H, dt, *J*≈1.5, 8.0 Hz), 6.69 (2H, m), 3.90 (1H, bs), 3.41 (1H, tt, *J*≈3.5, 9.5 Hz), 2.11 (2H, m), 1.79 (2H, m), 1.68 (1H, m), 1.45 (9H, s), 1.31 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ; LRMS 231, 216, 188, 134, 106; exact mass calcd for $C_{16}H_{25}N$ 231.1987, found 231.2021.

(2,5-Di-tert-butylphenyl)methylamine

IR (thin film) 3490, 2958, 1608, 1523, 1392, 1309, 1249 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.19 (1H, d, *J*=7.9 Hz), 6.71 (2H, m), 2.95 (3H, s), 1.43 (9H, s), 1.35 (9H, s); LRMS 219, 204, 91, 75, 57; HRMS exact mass calcd for $C_{15}H_{25}N$ 177.1517, found 177.1517.

Cyclohexyl-(2,5-di-tert-butylphenyl)amine

IR (thin film) 3467, 1566, 1417 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.15 (1H, d, *J*=8.2 Hz), 6.71 (1H, d, *J*≈1.9 Hz), 6.65 (2H, dd, *J*≈1.8, 8.2 Hz), 3.82 (1H, d, *J*≈7.0 Hz), 3.44 (1H, m), 1.79 (2H,

m), 1.67 (1H, m), 1.41 (9H, s), 1.31 (9H, s), 1.30 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.56, 144.77, 129.92, 125.94, 113.01, 109.51, 51.59, 34.25, 33.65, 33.33, 30.09, 26.11, 24.82; LRMS 287, 272, 244, 190; exact mass calcd for $C_{20}H_{33}N$ 287.2613, found 287.2609.

N-(2-tert-Butylphenyl)-2,N-dimethylacrylamide (2e)

(2-*tert*-Butylphenyl)methylamine (0.05 g, 3.07 mmol) was dissolved in CH_2Cl_2 (40 mL) followed by addition of methacroilyl chloride (0.90 mL, 9.21 mmol). Pyridine (0.50 mL, 6.14 mmol) was then added slowly. After 10 h at 25°C, the reaction was quenched with H_2O (100 mL) and extracted with CH_2Cl_2 (3×50 mL). The organic layer was washed with sat $NaHCO_3$ (2×50 mL), once with brine (20 mL) and dried over $MgSO_4$. Solvent evaporation gave the crude anilide as a yellow oil. Purification by flash chromatography on silica gel eluting with hexanes:ethyl acetate (7:1) to give the pure *N*-(2-*tert*-butylphenyl)-2,*N*-dimethylacrylamide as white crystals (68%): IR (thin film) 1651, 1620, 1489, 1439, 1364 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (1H, m), 7.27 (1H, m), 7.14 (1H, dt, *J*=1.4, 7.8 Hz), 6.98 (1H, m), 5.32 (1H (min), bs), 5.27 (1H (min), bs), 5.08 (1H (maj), bs), 4.90 (1H (maj), bs), 3.32 (3H (min), s), 3.24 (3H (maj), s), 2.07 (3H, (min), s), 1.78 (3H (maj), s), 1.41 (9H (min), s), 1.37 (9H (maj), s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.34, 170.56, 146.52, 145.64, 141.77, 141.34, 140.99, 140.05, 130.67, 130.06, 129.86, 128.37, 128.01, 127.73, 127.50, 126.62, 120.58, 115.59, 41.84, 40.15, 35.98, 35.43, 32.03, 31.29, 21.26, 19.90; LRMS 174, 91, 76, 57; exact mass calcd for $C_{11}H_{12}NO$ 174.0919, found 174.0900.

N-(2,5-Di-tert-Butylphenyl)-2,N-dimethylacrylamide (2e^m)

IR (thin film) 1651, 1620, 1469, 1455 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42, (1H, d, *J*=8.5 Hz), 7.27 (1H, d, *J*=8.5 Hz), 6.96 (1H, m), 5.31 (1H (min), s), 5.26 (1H (min), s), 5.02 (1H (maj), s), 4.93 (1H (maj), s), 3.32 (3H (min), s), 3.25 (3H (maj), s), 2.08 (3H (min), s), 1.78 (3H (maj), s), 1.41 (9H (min), s), 1.39 (9H (maj), s), 1.30 (9H (min), s), 1.25 (9H (maj), s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.85, 150.27, 149.56, 143.29, 142.38, 141.28, 140.86, 140.44, 129.66, 128.11, 127.76, 126.50, 124.94, 120.09, 42.04, 40.12, 35.57, 35.11, 33.96, 32.07, 31.39, 31.10, 30.93, 21.32, 20.03; LRMS 230, 188, 158, 82, 69, 57; exact mass calcd for $C_{15}H_{20}NO$ 230.1545, found 230.1553.

N-(2-tert-Butylphenyl)-N-methylacrylamide (2a)

IR (thin film) 1661, 1619, 1487, 1424 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (1H, dd, *J*=1.3, 8.0 Hz), 7.32 (1H, dt, *J*=1.5, 7.6 Hz), 7.23 (1H, dt, *J*=1.5, 7.6 Hz), 6.95 (1H, dd, *J*=1.5, 7.6 Hz), 6.35 (1H, dd, *J*=2.1, 16.9 Hz), 5.90 (1H, dd, *J*=10.2, 16.9 Hz), 5.45 (1H, dd, *J*=2.1, 10.3 Hz), 3.24 (3H, s), 1.34 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.00, 146.39, 140.96, 130.22, 128.89, 128.37, 128.24, 127.20, 126.75, 38.60, 35.46, 31.48; LRMS 202, 196, 175, 160, 132, 55; exact mass calcd for $C_{10}H_{10}NO$ 160.0762, found 160.0775.

But-2-enoic acid (2-tert-butylphenyl)methylamide (2b)

IR (thin film) 1666, 1632, 1487, 1248 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (1H, dd, *J*=1.4, 8.2 Hz), 7.26 (1H, dt, *J*=1.6, 7.6 Hz), 7.16 (1H, dt, *J*=1.5, 7.6 Hz), 6.89 (1H, dd, *J*=1.5, 7.6 Hz), 6.82 (1H, dq, *J*=6.8, 15.1 Hz), 5.52 (1H, dd, *J*=1.6, 15.2 Hz), 3.15 (3H, s), 1.60 (3H, dd, *J*=1.6, 6.8 Hz), 1.30 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.32, 146.39, 141.25, 140.21, 130.22, 128.76, 128.02, 127.07, 122.84, 38.41, 35.37, 31.39, 20.45, 17.35, 13.72; LRMS 216, 210, 174, 160, 148, 69; exact mass calcd for $C_{11}H_{12}NO$ 174.0919, found 174.1911.

But-2-enoic acid (2,5-di-tert-butylphenyl)methylamide (2b^m)

IR (thin film) 1655, 1622, 1350 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (1H, d, *J*=8.5 Hz), 7.32 (1H, dd, *J*=2.2, 8.4 Hz), 6.90 (2H, m), 5.57 (1H, dt, *J*=1.6, 14.9 Hz), 3.22 (3H, s), 1.68 (3H, dd, *J*=1.7, 7.0 Hz), 1.33 (9H, s), 1.28 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.09, 150.57, 143.52, 141.21, 140.53, 128.71, 127.44, 125.20, 123.29, 38.92, 35.37, 34.10, 31.80, 31.06, 17.73; LRMS 230, 190, 132, 69, 57; exact mass calcd for $C_{15}H_{20}NO$ 230.1544, found 230.1537.

N-(2-tert-Butylphenyl)-N-methyl-3-phenylacrylamide (2e)

IR (thin film) 1657, 1616, 1487, 1448, 1365 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.65 (1H, d, *J*=15.6 Hz), 7.59 (1H, dd, *J*=1.5, 8.2 Hz), 7.37 (1H, dt, *J*=1.5, 7.6 Hz), 7.25 (6H, m), 7.02 (1H, dd, *J*=1.5, 7.6 Hz), 6.17 (1H, d, *J*=15.6 Hz), 3.30 (3H, s), 1.38 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.80, 146.87, 141.44, 141.28, 135.00, 130.60, 129.34, 129.15, 128.56, 128.50, 127.63, 127.56, 39.02, 35.79, 31.78; LRMS 278, 236, 131, 103, 77, 57; exact mass calcd for $C_{16}H_{14}NO$ 236.1075, found 236.1059.

N-(2,5-Di-tert-butylphenyl)-N-methyl-3-phenylacrylamide (2e^m)

IR (thin film) 1659, 1614, 1495, 1396 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.65 (1H, d, *J*=15.7 Hz), 7.51 (1H, d, *J*=8.5 Hz), 7.37 (1H, dd, *J*=2.2, 8.5 Hz), 7.26 (6H, s), 6.99 (1H, d, *J*=2.2 Hz), 6.16 (1H, d, *J*=15.6 Hz), 3.31 (3H, s), 1.36 (9H, s), 1.28 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.06, 150.76, 143.64, 141.22, 141.05, 135.23, 129.31, 128.83, 128.57, 127.66, 127.43, 125.49, 119.05, 39.15, 35.40, 34.14, 31.84, 31.06; LRMS 292, 131, 103, 84, 57; exact mass calcd for $C_{20}H_{22}NO$ 292.1701, found 292.1718.

3-(4-Bromophenyl)-N-(2-tert-butylphenyl)-N-methylacrylamide (2d)

IR (thin film) 1649, 1613, 1483 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.58 (2H, m), 7.37 (3H, m), 7.25 (1H, dt, *J*=1.5, 7.2 Hz), 7.11 (1H, d, *J*=7.5 Hz), 7.01 (1H, dd, *J*=1.5, 7.2 Hz), 6.14 (1H, d, *J*=15.5 Hz), 3.30 (3H, s), 1.37 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.48, 146.81, 141.21, 133.84, 131.67, 130.51, 129.18, 129.02, 128.63, 127.53, 123.39, 119.41, 39.05, 35.76, 31.74; LRMS 316, 211, 209, 102, 57; exact mass calcd for $C_{16}H_{15}ONBr$ 314.0180, found 314.0144.

2-Methyl-but-2-enoic acid (2,5-di-tert-butylphenyl)methylamide (2f^m)

IR (thin film) 1632, 1397, 1356 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36 (1H, d, *J*=8.5 Hz), 7.22 (1H, dt, *J*=2.0, 5.8 Hz), 6.90 (1H, d, *J*=2.0 Hz), 5.80 (1H (min), q, *J*=5.8 Hz), 5.72 (1H (maj), q, *J*=5.8 Hz), 3.24 (3H (min), s), 3.21 (3H (maj), s), 1.92 (3H (min), s), 1.73 (3H (min), d, *J*=6.8 Hz), 1.47 (3H (maj), s), 1.40 (3H (maj), d, *J*=6.8 Hz), 1.34 (9H (min), s), 1.33 (9H (maj), s), 1.27 (9H (min), s), 1.24 (9H (maj), s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.24, 172.50, 150.18, 149.30, 143.25, 142.34, 141.86, 140.92, 132.96, 132.90, 130.53, 129.67, 129.53, 128.03, 127.93, 126.62, 125.78, 124.56, 42.19, 40.18, 35.59, 35.04, 34.04, 32.04, 31.45, 31.38, 31.10, 30.90, 30.58, 14.31, 13.63, 13.14; LRMS 244, 84, 49; exact mass calcd for $C_{16}H_{22}NO$ 244.1701, found 244.1701.

N-(2,5-Di-tert-butylphenyl)-2,N-dimethyl-3-phenylacrylamide (2g^m)

IR (thin film) 1642, 1493, 1431, 1383 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35 (2H, m), 7.27 (2H, m), 7.17 (2H, m), 6.94 (2H, m), 6.61 (1H, bs), 3.34 (3H (min), s), 3.30 (3H (maj), s), 2.20 (3H (min), s), 2.10 (3H (maj), d, *J*=1.3 Hz), 1.39 (9H (min), s), 1.35 (9H (maj), s), 1.29 (9H (min), s), 1.22 (9H (maj), s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.31, 172.56, 149.71, 142.48, 140.89, 140.47, 136.10, 135.67, 134.38, 133.42, 129.99, 129.79, 129.73, 129.02, 128.79, 128.50, 128.34, 127.98, 127.93, 127.29, 127.11, 125.01, 40.54, 35.72, 34.01, 32.20, 31.52, 31.16, 31.03, 22.59, 16.60, 14.05, 13.72; LRMS 306, 230, 216, 145, 117, 91; exact mass calcd for $C_{21}H_{24}NO$ 306.1858, found 306.1849.

N-(2-tert-Butylphenyl)-N-methylbenzamide (2h)

IR (thin film) 1620, 1372 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.60 (1H (maj), m), 7.53 (1H (min), m), 7.43 (2H, m), 7.32 (2H, m), 7.16 (4H, m), 3.40 (3H (maj), s), 3.26 (3H (min), s), 1.47 (9H (min), s), 1.23 (9H (maj), s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.60, 169.21, 146.48, 145.84, 142.38, 141.41, 136.42, 135.60, 130.98, 130.25, 130.05, 129.73, 129.44, 129.12, 128.36, 127.99, 127.78, 127.63, 127.24, 126.92, 126.72, 43.00, 40.56, 35.91, 35.51, 31.84, 31.44; LRMS 252, 224, 210, 105, 77; exact mass calcd for $C_{14}H_{12}NO$ 210.0919, found 210.0914.

N-(2-tert-Butylphenyl)-N-methylbenzamide (2h^m)

IR (thin film) 1637, 1355 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (1H (min), m), 7.46 (1H (maj), m), 7.06–7.24 (6H, m), 7.21 (d, 1H (min), *J*=2.2 Hz), 7.00 (1H (maj), d, *J*=2.2 Hz) 3.41 (3H (maj), s), 3.27 (3H (min), s), 1.46 (9H (min), s), 1.33 (9H (min), s), 1.24 (9H (maj), s), 1.22 (9H (maj), s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.04 (min), 169.48 (maj), 150.17 (min), 149.50 (maj), 143.05 (min), 142.38 (maj), 141.67 (min), 140.76 (maj), 136.56 (min), 135.77 (maj), 129.64, 129.46, 129.08, 128.76, 128.18, 128.05, 127.03, 126.76, 126.52, 124.72, 43.03 (min), 40.36 (maj), 35.33 (maj), 35.01 (min), 33.95 (min), 33.75 (maj), 31.76 (maj), 31.39 (min), 31.02 (min), 30.74 (maj); LRMS 308, 266, 105, 77; exact mass calcd for $C_{22}H_{29}NO$ 266.1545 (M−*t*-Bu), found 266.1547.

N-(2-tert-Butylphenyl)-N-ethyl-2-methylacrylamide (2i)

IR (thin film) 1634, 1616, 1478, 1432 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (1H, d, *J*=8.0 Hz), 7.27 (1H, dt, *J*=1.6, 8.5 Hz), 7.12 (1H, dt, *J*=1.6, 8.5 Hz), 6.98 (1H (min), d, *J*=7.5 Hz), 6.92 (1H (maj), dd, *J*=1.0, 7.7 Hz), 5.25 (1H, s), 5.02 (1H, s), 4.91 (1H, s), 4.37 (1H (maj), dq, *J*=7.0, 13.2 Hz), 4.03 (1H (min), dq, *J*=7.2, 14.6 Hz), 3.24 (1H (min), dq, *J*=7.1, 14.3 Hz), 2.87 (1H (maj), dq, *J*=7.0, 13.2 Hz), 2.08 (3H (min), s), 1.77 (3H (min), s), 1.37 (9H, s), 1.20 (3H, t, *J*=6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.59, 169.42, 146.16, 145.42, 140.85, 140.31, 139.21, 138.69, 131.74, 131.64, 130.34, 128.87, 127.79, 127.50, 126.26, 125.78, 119.51, 114.43, 47.76, 46.79, 35.88, 35.59, 32.07, 31.48, 21.03, 20.19, 14.50, 11.55; LRMS 230, 204, 188, 162, 132,69; exact mass calcd for $C_{12}H_{14}NO$ 188.1075, found 188.1079.

N-(2-tert-Butylphenyl)-N-cyclohexyl-2-methylacrylamide (2j)

IR (thin film) 1644, 1617, 1595, 1381 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (1H, d, *J*=8.5 Hz), 7.27 (2H, m), 7.11 (2H, m), 5.03 (1H, m), 4.87 (1H, s), 4.12 (1H, dt, *J*=3.3, 10.6 Hz), 2.50 (1H, m), 1.81 (1H, m), 1.73 (3H, s), 1.63 (2H, m), 1.42 (4H, m), 1.31 (9H, s), 1.05 (1H, m), 0.81 (1H, dq, *J*=3.2, 8.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.78, 147.14, 141.31, 136.59, 132.41, 130.90, 127.85, 125.39, 120.90, 57.91, 36.38, 32.67, 32.29, 30.74, 26.05, 25.90, 25.76, 21.14; LRMS 306, 284, 264, 242, 160, 132, 69; exact mass calcd for $C_{16}H_{30}NO$ 242.1545, found 242.1531.

N-(2-tert-Butylphenyl)-N-methylacetamide (2k)

IR (thin film) 1663, 1489, 1441, 1375 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (1H, dd, *J*=1.5, 8.0 Hz), 7.30 (1H, dt, *J*=1.5, 7.1 Hz), 7.22 (1H, dt, *J*=1.5, 7.6 Hz), 6.96 (1H, dd, *J*=1.5, 7.6 Hz), 3.17 (3H, s), 1.78 (3H, s), 1.37 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.97, 145.58, 141.89, 129.57, 128.85, 127.98, 127.08, 38.14, 35.27, 31.26, 22.42; LRMS 190, 179, 148, 132, 84, 49; exact mass calcd for $C_9H_{10}NO$ 148.0762, found 148.0764.

N-(2-tert-Butylphenyl)-N-methylpropionamide (2l)

IR (thin film) 1657, 1487, 1377 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (1H, dd, *J*=1.6, 8.0 Hz), 7.30 (1H, dt, *J*=1.6, 7.2 Hz), 7.22 (1H, dt, *J*=1.6, 7.2 Hz), 6.95 (1H, dd, *J*=1.6, 7.7 Hz), 3.17 (3H, s), 1.96 (2H, q, *J*=7.5 Hz), 1.35 (9H, s), 1.03 (3H, t, *J*=7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.60, 145.81, 141.60, 129.74, 129.66, 129.00, 128.08, 38.37, 35.46, 31.39, 27.86, 8.97; LRMS 220, 204, 190, 174, 162, 148, 132, 117, 91, 77, 70. 57; exact mass calcd for $C_{10}H_{12}NO$ 162.0919, (M–^{t}Bu) found 162.0920.

N-(2,5-Di-tert-butylphenyl)-N-methylpropionamide (2l^m)

IR (thin film) 1632, 1368, 1333 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (1H, d, *J*=8.4 Hz), 7.30 (1H, dd, *J*=1.2, 8.3 Hz), 6.91 (1H, d, *J*=2.1 Hz), 3.18 (3H, s), 1.96 (2H, q, *J*=7.5 Hz), 1.34 (9H, s), 1.28 (9H, s), 1.03 (3H, t, *J*=7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.96, 150.63, 142.74, 141.51, 128.76, 126.75, 125.07, 38.60, 35.27, 33.97, 31.61, 30.97, 28.15, 9.39; LRMS 260, 218, 188, 132, 70; exact mass calcd for $C_{14}H_{20}NO$ 218.1545, found 218.1561.

*Cyclohexane carboxylic acid (2-tert-butylphenyl)methylamide (**2m**)*

IR (thin film) 1705, 1607, 1431 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.54 (1H, dd, *J*=1.4, 8.0 Hz), 7.30 (1H, dt, *J*=1.5, 7.3 Hz), 7.20 (1H, dt, *J*=1.5, 7.6 Hz), 6.97 (1H, dd, *J*=1.5, 7.6 Hz), 3.14 (3H, s), 2.39 (1H, tt, *J*=3.7, 11.1 Hz), 1.93 (2H, m), 1.75 (1H, m), 1.65 (3H, m), 1.46 (2H, m), 1.36 (9H, s), 1.28 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.35, 146.10, 141.50, 129.93, 129.37, 128.27, 127.04, 42.81, 38.92, 31.84, 28.68, 25.59, 25.53, 25.50, 25.08; LRMS 258, 216, 128, 83, 73, 55; exact mass calcd for $C_{14}H_{18}NO$ 216.1388, found 216.1359.

*Cyclohexane carboxylic acid (2,5-di-tert-butylphenyl)methylamide (**2m^m**)*

IR (thin film) 1660, 1378, 1253 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45 (1H, d, *J*=8.6 Hz), 7.31 (1H, dd, *J*=1.2, 8.6 Hz), 6.94 (1H, d, *J*=1.2 Hz), 3.15 (3H, s), 1.93 (1H, tt, *J*=2.8, 10.9 Hz), 1.61 (7H, m), 1.35 (9H, s), 1.28 (9H, s), 1.18 (1H, m), 0.98 (1H, m), 0.82 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.12, 149.87, 142.73, 141.15, 128.72, 126.84, 124.87, 42.26, 38.60, 35.24, 33.87, 31.68, 30.79, 30.19, 28.15, 25.40, 25.28, 24.98; LRMS 272, 258, 238, 230, 216, 148, 128, 110, 99, 83, 73, 68, 55, 50; exact mass calcd for $C_{14}H_{18}NO$ 216.1388 (M–^{t}Bu), found 216.1359.

*N-(2,5-Di-tert-butylphenyl)-2,2,N-trimethylpropionamide (**2n^m**)*

IR (thin film) 1632, 1503, 1480, 1362 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41 (1H, d, *J*=8.5 Hz), 7.28 (1H, dd, *J*=2.2, 8.5 Hz), 6.91 (1H, d, *J*=2.2 Hz), 3.12 (3H, s), 1.37 (9H, s), 1.27 (9H, s), 0.99 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.86, 149.35, 142.05, 141.53, 129.86, 127.17, 125.04, 42.45, 41.06, 35.72, 33.91, 32.26, 30.96, 29.68; LRMS 246, 204, 190, 132, 57; exact mass calcd for $C_{16}H_{24}NO$ 246.1858, found 246.1835.

2,5-Di-tert-butylphenylpentylamine

IR (thin film) 3494, 3068, 2956, 2908, 2816, 1604, 1575, 1506, 1446, 1301, 1261, 1172, 1051, 746, 486 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.17 (1H, d, *J*=8.7 Hz), 6.70 (2H, bs), 3.78 (1H, bs), 3.19 (1H, t, *J*=7.0 Hz), 1.74–1.65 (2H, m), 1.48–1.19 (4H, m), 1.41 (9H, s), 1.31 (9H, s), 0.94 (3H, t, *J*=7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.9, 146.4, 130.3, 125.9, 113.7, 109.3, 44.7, 34.5, 33.9, 31.5, 30.2, 29.8, 29.6, 22.7, 14.2; LRMS 275, 260, 218, 205, 190, 132, 57; exact mass calcd for $C_{19}H_{33}N$ 275.2613, found 275.2608

*But-2-enoic acid (2,5-di-tert-butylphenyl)pentylamide (**2o^m**)*

IR (thin film) 2964, 2871, 1788, 1730, 1664, 1627, 1442, 1408, 1363, 1288, 1240, 1078, 970 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.50 (1H, d, *J*=8.4 Hz), 7.35 (1H, dd, *J*=4.5, 8.4 Hz), 6.93–6.86 (2H, m), 5.59 (1H, dd, *J*=1.6, 14.9 Hz), 4.33–4.29 (1H, m), 2.78–2.75 (1H, m), 1.81–1.73 (1H, m), 1.69 (3H, dd, *J*=1.6, 7.0 Hz), 1.54–1.38 (2H, m), 1.35–1.26 (3H, m), 1.32 (9H, s), 1.29 (9H, s), 0.90–0.85 (3H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.0, 149.7, 143.5, 140.4, 139.4, 129.5, 129.2, 125.2, 123.7, 51.1, 35.7, 34.0, 32.2, 31.1, 29.3, 26.8, 22.5, 17.8, 14.0; LRMS 286, 216, 148, 69, 57; exact mass calcd for $C_{19}H_{36}NO$ 286.2171 (M–C_4H_9), found 286.2172.

Enantiomer separation and determination of rotation barriers

Solvents were either HPLC grade from Merck or from Carlo Erba, or were purified as usual. Dead times (t_0) were estimated by using 1,3,5-tri-*tert*-butylbenzene. The thermal racemizations of each amide were carried out in triplicate using the first and the second eluted enantiomers with 2-butanol as solvent except for amide (**43**) in which 2-propanol was used.

Equipment: The analytical HPLC system consisted of a Shimadzu LC-10AD pump, an SPD-6AV UV detector operated at 254 nm, and an LC-R6A chromatopac recorder. The preparative system used was a Shimadzu LC 6 AD with a C-R 4A chromatopac recorder or a Shimadzu LC 8A, with a simple register ECB RB 201, both with an SPD-6AV UV detector. The rotational barrier was determined using a Chiralyser polarimetric detector. A Rheodyne 7125 injector was used in all cases. The loops used were 20 μL, 500 μL or 1 mL.

Preparation of stationary phases. The analytical (150×4.6 mm ID) and preparative (250×20 mm ID) HPLC columns of cellulose tris(3,5-dimethylphenylcarbamate) have been used before.[25] The Amylose tris[(*S*)-1-phenylethylcarbamate] was prepared and the support coated as described elsewhere.[24] This material was used to pack two analytical (150×4.6 mm ID) (2.7 g) columns, one using APS-Hypersil (120 Å, 5 μm) and the other APS-Nucleosil (5000 Å, 7 μm) as support; and a semi-preparative column (250×7.0 mm ID) (12.3 g) coated with APS-Hypersil (120 Å, 5 μm). These columns were packed at 7500 psi on a Shandon pump using a slurry of hexane:Nujol (3:2) and hexane:2-propanol (80:20 v:v) for the packing.

2-[2-Methylaminophenyl]propan-2-ol (8a)

Methyl magnesium bromide (3.0 M in Et_2O, 190 mL, 0.57 mol) was slowly added to *N*-methylisatoic anhydride (20.0 g, 0.113 mol) in THF (350 mL) at −78°C. The reaction temperature was allowed to slowly rise to room temperature. After 9 h the reaction was quenched with H_2O, and stirring was continued for 16 h. The reaction mixture was acidified with 1 N HCl, and the acidic solution was washed with EtOAc. The acidic solution was then basified with 2 N NaOH to a pH of about 8 and extracted with EtOAc. These extracts were dried over $MgSO_4$ and concentrated under vacuum to yield a tan solid in 71% yield (13.4 g): m.p. 64–66°C; ^{1}H NMR ($CDCl_3$) δ 7.21 (td, 1H, *J*=1.29 Hz, 10.86 Hz), 7.14 (dd, 1H, *J*=1.41 Hz, 7.65 Hz), 6.61–6.67 (m, 2H), 2.85 (s, 3H), 1.67 (s, 6H), 1.30 (brs, 1H); ^{13}C NMR ($CDCl_3$) δ 148.2, 130.0, 128.7, 125.4, 115.8, 110.9, 74.6, 30.5, 29.3; IR 3427, 3334, 2914, 2873, 2723, 2364, 2339, 1600, 1510, 1458, 1375, 1313, 1151, 1164, 949, 860, 736, 488, 434 cm^{-1}; LRMS 77, 78, 79, 91, 105, 107, 132, 134, 135, 165, 167; exact mass calcd for $C_{10}H_{15}NO$ 165.1153, found 165.1147.

Methyl-[2-(1-methyl-1-trimethylsilanyloxyethyl)phenyl]amine (9a)

Triethylamine (15.2 mL, 109 mmol) was added to 2-(2-methylaminophenyl)propan-2-ol (12.0 g, 72.6 mmol) in THF (150 mL) and after 5 min, chlorotrimethylsilane (8.50 mL, 110 mmol) was added. After 8 h, the solvent was concentrated under vacuum and the resultant yellow oil was purified by flash chromatography to give 60% yield of a pale yellow liquid (11.1 g): ^{1}H NMR ($CDCl_3$) δ 7.16 (td, 1H, 1.41, 7.74 Hz), 7.07 (dd, 1H, 1.62, 6.18 Hz), 6.63–5.58 (m, 2H), 5.77 (brd, 1H, 3.87 Hz), 2.85 (d, 3H, 5.28 Hz), 1.67 (s, 6H), 0.00 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 148.1, 128.2, 124.6, 115.6, 110.3, 76.7, 30.3, 30.1, 1.8; IR 3411, 2981, 2807, 1602, 1515, 1459, 1315, 1253, 1145, 1010, 845, 904, 740, 472 cm^{-1}; LRMS 57, 75, 85, 97, 105, 117, 132, 147, 172, 222, 237; exact mass calcd for $C_{13}H_{23}NOSi$ 237.1549, found 237.1561.

Methyl-[2-(1-methyl-1-triisopropylsilanyloxyethyl)phenyl]amine (9b)

Sodium hydride (53 mg 60%, 1.3 mmol) was added to 2-(2-methylaminophenyl)propan-2-ol (100 mg, 0.605 mmol) in THF (0.6 mL) and after 5 min. TIPSCl (285 μL, 1.3 mmol) was added. The reaction was quenched with H_2O after 16 h and washed with saturated $NaHCO_3$. The organic layer was concentrated under vacuum and the resulting brown oil was purified by flash chromatography with hexanes to give 47% yield of a colorless oil (92 mg): ^{1}H NMR ($CDCl_3$) δ 7.16 (td, 1H, 0.93 Hz, 7.30 Hz), 7.10 (dd, 1H, 1.44 Hz, 7.98 Hz), 6.63–6.58 (m, 2H), 5.85 (brd, 1H, 4.65 Hz), 2.81 (d, 3H, 5.22 Hz), 1.72 (s, 6H), 1.07–0.90 (m, 21H); ^{13}C NMR ($CDCl_3$) δ 148.5, 130.9, 128.3, 124.6, 115.5, 110.4, 76.8, 30.4, 29.8, 18.2, 13.6; IR 3407, 2945, 2863, 3072, 2358, 2343, 1600, 1514, 1459, 1311, 1240, 1171, 1143, 1012, 881, 802, 748, 679 cm^{-1}; LRMS 45, 61, 75, 85, 103, 117, 132, 148, 167, 264, 278, 306, 321; exact mass calcd for $C_{19}H_{35}NOSi$ 321.2488, found 321.2501.

N-Methyl-N-[2-(1-methyl-1-trimethylsilanyloxyethyl)phenyl]-3-phenylpropionamide (10f)

Dimethylaminopyridine (2.6 mg, 0.021 mmol) was added to a mixture of methyl-[2-(1-methyl-1-trimethylsilanyloxyethyl)phenyl]amine (500 mg, 2.10 mmol), triethylamine (320 μL, 2.3 mmol), and hydrocinnamoyl chloride (340 μL, 2.3 mmol) in THF (20 mL) at 0°C. After 30 min the reaction was quenched with water and the solvent was concentrated under vacuum. The crude product was purified

by flash chromatography with hexanes:ethyl acetate (1 : 1) to give 51% yield of a colourless liquid (392 mg): ^{1}H NMR ($CDCl_3$) δ 7.67 (dd, 1H, 1.50, 8.16 Hz), 7.31 (td, 1H, 1.50 Hz, 7.92 Hz), 7.25–7.14 (m, 4H), 7.07 (dd, 2H, 1.53 Hz, 8.22 Hz), 6.69 (d, 1H, 7.68 Hz), 3.19 (s, 3H), 3.03–2.83 (m, 2H), 2.33–2.26 (m, 2H), 1.60 (s, 6H), 0.17 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 172.6, 145.5, 141.1, 140.0, 129.8, 128.6, 128.3, 128.1, 125.8, 75.8, 38.3, 36.8, 32.2, 31.8, 31.4, 2.5; IR 3440, 3060, 3023, 2964, 2538, 2331, 1946, 1816, 1731, 1656, 1493, 1450, 1378, 1253, 1167, 1070, 906, 840, 754, 698 cm^{-1}; LMRS: 354, 279, 230, 196, 132, 117; exact mass calcd for $C_{21}H_{28}NO_2Si$ 354.1889 (M–CH_3), found 354.1863.

Removal of auxiliary from N-methyl-N-*[2-(1-methyl-1-trimethylsilanyloxy-ethyl)-phenyl]-3-phenylpropionamide (10g); Synthesis of 2-(2-methylamino-phenyl)propan-2-ol (8a) and hydrocinnamic acid (12)*

TBAF (0.75 mL, 1 M soln in THF, 0.75 mmol) was added to *N*-methyl-*N*-[2-(1-methyl-1-trimethylsilanyloxyethyl)phenyl]-3-phenyl-propionamide (100 mg, 0.271 mmol) in THF (7 mL) and the mixture was stirred for 30 min. Acetone (4 mL) and 1 N HCl (6 mL) were added and the mixture was stirred for 1 h. The reaction mixture was washed with saturated $NaHCO_3$ and the organic layer was evaporated by rotary evaporator to give 31% (14 mg) 2-(2-methylaminophenyl)propan-2-ol. The $NaHCO_3$ layers were acidified and extracted with EtOAc to give 99% yield of hydrocinnamic acid (40 mg). The ^{1}H NMR spectrum of 2-(2-methylaminophenyl)propan-2-ol matched that described above, and the ^{1}H NMR and IR spectra for hydrocinnamic acid matched those of the commercially available compound.

N-Methyl-N-[2-(1-methyl-1-trimethylsilanyloxyethyl)phenyl]acrylamide (10d)

Pyridine (190 μL, 2.35 mmol) was slowly added to methyl-[2-(1-methyl-1-trimethylsilanyloxyethyl)phenyl]amine (500 mg, 2.11 mmol) and acryloyl chloride (175 μL, 2.15 mmol) at ~5°C, and the reaction temperature was warmed to room temperature over 30 min. After 13 h, water was added to quench the reaction. The mixture was washed with 0.1 N HCl, then saturated $NaHCO_3$ and brine. The organic layer was dried with $MgSO_4$ and concentrated *in vacuo* to give a clear oil that was purified by flash chromatography with hexanes:ethyl acetate (10:1). A colorless liquid was obtained in 43% yield (312 mg): ^{1}H NMR ($CDCl_3$) δ 7.73 (dd, 1H, 1.62, 7.92 Hz), 7.36 (td, 1H, 1.20, 7.26 Hz), 7.31 (td, 1H, 1.65, 4.32 Hz), 7.26 (td, 1H, 2.97, 4.65 Hz), 6.97 (dd, 1H, 1.47, 7.68 Hz), 6.35 (dd, 1H, 2.04, 16.8 Hz), 5.90 (dd, 1H, 10.08, 16.65 Hz), 5.46 (dd, 1H, 2.16 Hz, 10.38 Hz), 3.25 (s, 3H), 1.59 (d, 6H, 1.26 Hz), 0.13 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 165.6, 145.9, 139.4, 130.0, 128.5, 128.4, 128.2, 128.0, 126.7, 75.5, 38.2, 37.2, 31.7, 2.2; IR 3064, 2956, 1930, 1666, 1620, 1483, 1423, 1396, 1357, 1348, 1249, 1162, 1124, 1072, 1034, 912, 845, 760 cm^{-1}; LRMS 45, 55, 73, 91, 117, 132, 146, 160, 196, 206, 276; exact mass calcd for $C_{16}H_{25}NO_2Si$ 276.1420 (M–CH_3), found 276.1417.

N-Methyl-N-[2-(1-methyl-1-trimethylsilanyloxyethyl)phenyl]-3-phenylacrylamide (10a)

Pyridine (205 μL, 2.53 mmol) was added over 1 h to methyl-[2-(1-methyl-1-trimethylsilanyloxyethyl)phenyl]amine (500 mg, 2.11 mmol) and cinnamoyl chloride (387 mg, 2.32 mmol) as described for *N*-methyl-*N*-[2-(1-methyl-1-trimethylsilanyloxyethyl)phenyl]acrylamide, except that the reaction took only 1 h at room temperature. The crude product was purified by flash chromatography with hexanes:ethyl acetate (10:1) to give 26% yield of the pure product (205 mg): ^{1}H NMR ($CDCl_3$) δ 7.80 (dd, 1H, 1.41, 7.98 Hz), 7.66 (d, 1H, 15.51 Hz), 7.41 (t, 1H, 7. 29 Hz), 7.30 (td, 1H, 1.56, 7.62 Hz), 7.26 (s, 5H), 7.03 (dd, 1H, 1.38silica, 7.68 Hz), 6.18 (d, 1H, 15.7 Hz), 3.30 (s, 3H), 1.62 (s, 6H), 0.11 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 166.5, 146.4, 141.4, 139.7, 135.0, 130.4, 129.4, 128.9, 128.5, 128.4, 127.7, 118.9, 75.8, 38.6, 32.4, 31.9, 29.3, 2.5; IR 3058, 2960, 1656, 1616, 1361, 1247, 1026, 845, 758 cm^{-1}; LRMS 73, 91, 103, 117, 131, 146, 206, 236, 309, 352; exact mass calcd for $C_{22}H_{30}NO_2Si$ 352.1710 (M–CH_3), found 352.1721.

N-Methyl-N-[2-(1-methyl-1-triisopropylsilanyloxyethyl)phenyl]-3-phenylacrylamide (10b)

Pyridine (19 μL, 0.23 mmol) was added slowly to methyl-[2-(1-methyl-1-triisopropylsilanyloxyethyl)phenyl]amine (47 mg, 0.15 mmol) and cinnamoyl chloride (39 mg, 0.23 mmol) as described for *N*-methyl-*N*-[2-(1-methyl-1-trimethylsilanyloxyethyl)phenyl]acrylamide, except that the reaction took only 2 h between −5 and 0°C. Pure product was was obtained by flash chromatography with hexanes:ethyl acetate (10:1) in 43% yield (31 mg): ^{1}H NMR ($CDCl_3$) δ 8.07 (d, 1H, 7.71 Hz), 7.67 (d, 1H, 15.51 Hz), 7.42 (t, 1H, 7.41 Hz), 7.30 (t, 1H, 7.38 Hz), 7.26 (s, 5H), 7.03 (d, 1H, 7.29 Hz), 6.18 (d, 1H, 15.5 Hz), 3.30 (s, 3H), 1.63 (d, 6H, 6.75 Hz), 1.05 (brs, 21H); ^{13}C NMR ($CDCl_3$) δ 167.0, 147.2, 141.9, 139.2, 135.1, 130.1, 129.7, 128.7, 128.5, 128.0, 127.5, 118.7, 74.9, 38.8, 32.6, 31.7, 18.6, 13.7; IR 3056, 2927, 2868, 1664, 1365, 1167, 1076, 1045 cm^{-1}.

2,4-Dimethyl-3-(2-methylaminophenyl)pentan-3-ol (8b)

Isopropyl magnesium chloride (2.0 M in THF, 75 mL, 0.15 mol) was slowly added to *N*-methylisatoic anhydride (10.0 g, 0.0564 mol) in THF (100 mL) at −78°C. The reaction temperature was allowed to slowly rise to room temperature, at which point the solution was refluxed for 3 h. The reaction was quenched with H_2O, and stirring was continued for 1 h. The reaction mixture was acidified with 1 N HCl, and the acidic solution was washed with EtOAc. The acidic solution was then basified with 2 N NaOH to a pH of about 8 and extracted with EtOAc. These extracts were dried over $MgSO_4$ and concentrated under vacuum to yield a brown oil which was a 2.2:1 mixture of the desired product and the product of mono-addition. Repeated flash chromatography with hexanes:ethyl acetate (20:1) removed nearly all traces of the mono-addition product and produced 28.4% yield of a tan solid. A small amount of the tan solid was recrystallized for analysis: ^{1}H NMR ($CDCl_3$) δ 7.14 (td, 1H, *J*=1.24 Hz, 7.61 Hz), 6.93 (d, 1H, 7.65 Hz), 6.70–6.63 (m, 2H), 4.48 (brs, 1H), 2.79 (s, 3H), 2.33 (septet, 2H, 6.77 Hz), 0.94 (d, 6H, 6.69 Hz), 0.83 (d, 6H, 6.78 Hz); ^{13}C NMR ($CDCl_3$) δ 150.1, 128.4, 127.6, 124.6, 115.8, 112.8, 86.1, 76.4, 35.6, 31.6, 17.9, 16.7; IR 3423, 3065, 2978, 2881, 1602, 1583, 1518, 1464, 1309, 1174, 1091 cm^{-1}.

[2-(1-Isopropyl-2-methyl-1-trimethylsilanyloxypropyl)phenyl]methylamine (9c)

2,4-Dimethyl-3-(2-methylaminophenyl)pentan-3-ol (500 mg, 2.26 mmol) and 2,4,6-collidine (900 μL, 6.81 mmol) were dissolved in methylene chloride (25 mL) and the solution was cooled to −78°C. To this solution, TLRMSOTf (1.30 mL, 6.73 mmol) was slowly added and stirring was continued for 1 h. The reaction mixture was washed with brine and concentrated. The resulting reddish-brown solid was flash chromatographed with hexanes:ethyl acetate (20:1), and subsequently with hexanes:ethyl acetate (50:1) to provide 31% of the product (204 mg) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.10 (td, 1H, *J*=1.14 Hz, 7.53 Hz), 6.92 (d, 1H, 7.92 Hz), 6.60–6.52 (m, 2H), 6.28 (brs, 1H), 2.76 (d, 3H, 5.25 Hz), 2.42 (septet, 2H, 6.80 Hz), 0.96 (d, 6H, 6.81 Hz), 0.84 (d, 6H, 6.84 Hz), 0.32 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 150.8, 128.3, 127.3, 124.1, 114.4, 111.2, 93.2, 35.4, 30.3, 18.1, 17.4, 3.3; IR 3464, 3080, 2966, 2883, 1172 cm^{-1}.

N-[2-(1-Isopropyl-2-methyl-1-trimethylsilanyloxypropyl)phenyl]-N-methyl-3-phenylacrylamide (10c)

Pyridine (41 μL, 0.51 mmol) was added slowly to [2-(1-isopropyl-2-methyl-1-trimethylsilanyloxypropyl)phenyl]methylamine (50 mg, 0.17 mmol) and cinnamoyl chloride (43 mg, 0.25 mmol) as described for *N*-methyl-*N*-[2-(1-methyl-1-trimethylsilanyloxyethyl)phenyl]acrylamide, except that the reaction was finished after 30 min. The resulting off-white solid was flash chromatographed with 10:1 hexanes:ethyl acetate to provide 72% of the product (204 mg) as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.64 (d, 1H, *J*=15.60 Hz), 7.36–7.22 (m, 8H), 6.93 (dd, 1H, *J*=1.11 Hz, 6.88 Hz), 6.41 (d, 1H, *J*=15.60 Hz), 3.29 (s, 3H), 2.49–2.39 (m, 2H), 1.04 (d, 3H, *J*=6.69 Hz), 1.03 (d, 3H, *J*=6.84 Hz), 0.84–0.80 (m, 6H), 0.22 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 166.4, 143.0, 141.6, 140.2, 135.6, 132.5, 129.2, 128.8, 128.6, 127.8, 127.7, 127.1, 120.6, 90.4, 39.6, 37.0, 36.7, 19.1, 19.0, 18.7,

17.6, 3.5; IR 3068, 3028, 2974, 1658, 1612, 1373, 1070, 835 cm^{-1}; LRMS 408, 380, 236, 202, 160, 144, 131, 118, 103, 91, 73; exact mass calcd for $C_{26}H_{37}NO_2Si$ 408.2359 (M − CH_3), found 408.2357.

N-*[2-(1-Isopropyl-2-methyl-1-trimethylsilanyloxypropyl)phenyl]-N-methyl acrylamide (10e)*

^1H NMR ($CDCl_3$) δ 7.26–7.17 (m, 2H), 6.84 (d, 1H, *J*=7.3 Hz), 6.31 (d, 1H, *J*=16.7 Hz), 6.07 (dd, 1H, *J*=10.2, 16.7 Hz), 5.39 (d, 1H, *J*=10.1 Hz), 3.21 (s, 3H), 2.43–2.31 (m, 2H), 0.98 (t, 3H, *J*=7.3 Hz), 0.75 (d, 3H, *J*=6.4 Hz), 0.19 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 166, 142.8, 141.5, 132.4, 130.0, 128.9, 127.6, 127.1, 126.1, 90.4, 77.4, 39.6, 37.0, 36.8, 19.0, 18.7, 17.7, 3.6; IR 3074, 2964, 2902, 1647, 1612, 1421, 1251, 1103, 1070 cm^{-1}.

Representative nitrile oxide addition with N-*(2-tert-butylphenyl)-N-methylacrylamide (2a^m)*

N-(2-*tert*-Butylphenyl)-*N*-methylacrylamide (0.25 g, 1.15 mmol) was dissolved in CH_2Cl_2 (15 mL) followed by addition of *t*-butyl oxime chloride (0.23 g, 1.73 mmol) and TEA (0.40 mL, 2.88 mmol). After 3 h, the reaction was complete by TLC and was quenched with H_2O (30 mL). The mixture was extracted with Et_2O (3×50 mL) and the organic layer was washed once with brine (30 mL) and dried over $MgSO_4$. Solvent evaporation gave the crude products which were purified by flash chromatography on silica gel eluting with hexanes:ethyl acetate (5:1) to give the pure product as an 8:1 mixture of diastereomers in 96% yield.

3-tert-Butyl-4,5-dihydro-isoxazole-5-carboxylic acid (2-tert-butylphenyl)methylamide (13a)

IR (thin film) 1659, 1474, 1429 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.50 (1H, dd, *J*=1.8, 7.9 Hz), 7.28 (3H, m), 4.68 (1H, dd, *J*=7.5, 10.7 Hz), 3.52 (1H, dd, *J*=7.5, 16.4 Hz), 3.24 (3H, s), 2.80 (1H, dd, *J*=10.3, 16.5 Hz), 1.33 (9H, s), 1.19 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.39, 165.47, 145.61, 1140.44, 131.64, 128.80, 128.50, 127.62, 75.87, 39.38, 36.76, 35.62, 32.78, 31.68, 27.92; LRMS 285, 259, 160, 134; exact mass calcd for $C_{25}H_{19}N_2O_2$ 259.1447 found 259.1475.

3-tert-Butyl-4,5-dihydro-isoxazole-5-carboxylic acid (2-tert-butylphenyl)methylamide (14a)

IR (thin film) 1659, 1470, 1428 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.59 (1H, dd, *J*=1.4, 8.1 Hz), 7.34 (1H, dt, *J*=1.5, 7.8 Hz), 7.22 (1H, dt, *J*=1.3, 7.8 Hz), 6.86 (1H, dd, *J*=1.3, 7.8 Hz), 4.69 (1H, dd, *J*=8.8, 10.7 Hz), 3.22 (3H, s), 3.21 (1H, dd, 9.0, 16.4 Hz), 2.81 (1H, dd, *J*=10.9, 16.4 Hz), 1.41 (9H, s), 1.17 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.87, 164.37, 147.07, 140.21, 130.19, 129.90, 128.87, 127.37, 75.70, 39.25, 39.12, 36.17, 32.81, 31.88, 28.03; LRMS 259, 160, 126; exact mass calcd for $C_{15}H_{19}N_2O_2$ 259.1447 found 259.1450.

3-Phenyl-4,5-dihydro-isoxazole-5-carboxylic acid (2,5-di-tert-butylphenyl)methylamide (13a^m)

^1H NMR ($CDCl_3$) δ 7.42 (d, 1H, *J*=8.4 Hz), 7.33 (dd, 1H, *J*=2.4, 8.4 Hz), 7.20 (d, 1H, *J*=2.4 Hz), 4.69 (dd, 1H, *J*=6.6, 10.8 Hz), 3.46 (dd, 1H, *J*=6.6, 16.8 Hz), 3.24 (s, 3H), 2.82 (dd, 1H, *J*=10.8, 16.8 Hz), 1.33 (s, 18H), 1.17 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 170.0, 165.6, 151.1, 142.5, 140.4, 128.9, 128.2, 125.7, 75.8, 39.5, 37.2, 35.4, 34.3, 33.0, 31.8, 31.1, 28.1; LRMS (two isomers) 315, 216, 190, 147, 126, 84, 57; exact mass calcd for $C_{19}H_{27}N_2O_2$ 315.2072 (M−C_4H_9), found 315.2059.

3-Phenyl-4,5-dihydro-isoxazole-5-carboxylic acid (2,5-di-tert-butylphenyl)methylamide (14a^m)

^1H NMR ($CDCl_3$) δ 7.49 (d, 1H, *J*=8.6 Hz), 7.33 (dd, 1H, *J*=2.2, 8.4 Hz), 6.80 (d, 1H, *J*=2.2 Hz), 4.67 (dd, 1H, *J*=9.2, 10.6 Hz), 3.24–3.19 (m, 4H), 2.76 (dd, 1H, *J*=10.6, 16.3 Hz), 1.39 (s, 9H), 1.29 (s, 9H), 1.16 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 171.2, 164.3, 150.6, 143.7, 140.0, 129.9, 127.0, 125.9, 76.1, 39.5, 39.3, 35.8, 34.2, 33.0, 32.0, 29.8, 28.2.

3-tert-Butyl-4,5-dihydro-isoxazole-5-carboxylic acid methyl-[2-(1-methyl-1-trimethylsilanyloxyethyl)-phenyl]amide (15d)

^1H NMR ($CDCl_3$) δ 7.60 (dd, 1H, *J*=4.8, 7.1 Hz), 7.38–7.24 (m, 3H), 4.70 (dd, 1H, *J*=7.4, 10.6 Hz), 3.57 (dd, 1H, *J*=7.5, 16.4 Hz), 3.24 (s, 3H), 2.79 (dd, 1H, *J*=10.6, 16.4 Hz), 1.60 (s, 3H), 1.59 (s, 3H), 1.19 (s, 9H), 0.15 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 168.8, 165.8, 145.2, 139.0, 128.8, 128.5, 128.1,

76.3, 76.2, 39.2, 36.9, 33.0, 32.5, 32.3, 28.2, 2.8; IR 3058, 2962, 1664, 1479, 1263, 1162, 1026 cm^{-1}; LMRS 375, 259, 173, 160; exact mass calcd $C_{26}H_{31}N_2O_3Si$ 375.2104 ($M-CH_3$), found 375.2106.

3-tert-Butyl-4,5-dihydro-isoxazole-5-carboxylic acid methyl [2-(1-methyl-1-trimethylsilanyloxyethyl)-phenyl]amide (16d)

^1H NMR ($CDCl_3$) δ 7.72 (dd, 1H, *J*=1.3, 8.1 Hz), 7.37 (t, 1H, *J*=7.6 Hz), 7.27 (td, 1H, *J*=1.3, 7.6 Hz), 6.87 (dd, 1H, *J*=1.2, 8.4 Hz), 4.66 (dd, 1H, *J*=8.8, 10.3 Hz), 3.23 (s, 3H), 3.20 (dd, 1H, *J*=8.8, 16.8 Hz), 2.83 (dd, 1H, *J*=10.9, 16.4 Hz), 1.68 (s, 3H), 1.66 (s, 3H), 1.17 (s, 9H), 0.15 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 170.8, 164.3, 146.7, 139.0, 129.9, 129.7, 129.0, 128.3, 76.3, 75.8, 39.5, 39.0, 33.0, 32.5, 32.4, 28.2, 2.7; IR 2962, 1745, 1672, 1249, 1166, 1027 cm^{-1}; LMRS 375, 301, 276, 259, 175, 160; exact mass calcd for $C_{26}H_{31}N_2O_3Si$ 375.2014 ($M-CH_3$), found 375.2106.

3-tert-Butyl-4,5-dihydro-isoxazole-5-carboxylic acid [2-(1-isopropyl-2-methyl-1-trimethylsilanyloxypropyl)-phenyl]methylamide (15e)

^1H NMR ($CDCl_3$) δ 7.28–7.19 (m, 4H), 4.81 (dd, 1H, *J*=8.0, 10.5 Hz), 3.51 (dd, 1H, *J*=8.0, 16.3 Hz), 3.24 (s, 3H), 2.75 (dd, 1H, *J*=10.6, 16.2 Hz), 2.42 (m, 2H), 1.30 (d, 2H, *J*=12.7 Hz), 1.20 (s, 9H), 1.01 (m, 6H), 0.77 (m, 6H), 0.23 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 168.8, 165.7, 141.9, 140.6, 133.2, 128.6, 128.0, 127.5, 90.6, 76.3, 39.9, 37.7, 36.9, 36.8, 33.1, 28.3, 18.8, 18.7, 18.5, 17.8, 3.8; IR 3015, 2965, 2875, 1664, 1251, 1102, 1068 cm^{-1}.

3-tert-Butyl-4,5-dihydro-isoxazole-5-carboxylic acid [2-(1-isopropyl-2-methyl-1-trimethylsilanyloxypropyl)-phenyl]methylamide (16e)

^1H NMR ($CDCl_3$) δ 7.33 (td, 1H, *J*=1.7, 6.9 Hz), 7.29–7.20 (m, 2H), 6.73 (dd, 1H, *J*=1.6, 7.4 Hz), 4.78 (dd, 1H, *J*=9.4, 10.7 Hz), 3.24 (s, 3H), 3.21 (dd, 1H, *J*=9.2, 16.3 Hz), 2.85 (dd, 1H, *J*=10.7, 16.3 Hz), 2.49–2.34 (m, 2H), 1.25–1.19 (m, 2H), 1.18 (s, 9H), 1.04 (d, 3H, *J*=6.7 Hz), 1.00 (d, 3H, *J*=6.9 Hz), 0.86 (d, 3H, *J*=6.7 Hz), 0.76 (d, 3H, *J*=6.8 Hz), 0.28 (s, 9H).

Acknowledgements

The Pittsburgh group thanks the National Institutes of Health for funding. The Brazilian Group thanks FAPESP, CAPES and CNPq (A.L.G.P.) for funding.

References

1. (a) Seyden-Penne, J. *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*; Wiley: NY, 1995. (b) Nógrády, M. *Stereoselective Synthesis*; VCH: WeinHeim, 1995. (c) Procter, G. *Asymmetric Synthesis*; Oxford University Press: Oxford, 1996.
2. Rosini, C.; Franzini, L.; Raffaelli, A.; Salvadori, P. *Synthesis* **1992**, 503.
3. Ito, Y. N.; Ariza, X.; Beck, A. K.; Bohac, A.; Ganter, C.; Gawley, R. E.; Kühnle, F. N. M.; Tuleja, J.; Wang, Y. M.; Seebach, D. *Helv. Chim. Acta* **1994**, *77*, 2071.
4. Seebach, D.; Sting, A. R.; Hoffmann, M. *Angew. Chem. Int. Ed. Eng.* **1997**, *35*, 2708.
5. Reviews: (a) Noyori, R.; Kitamura, M. In *Modern Synthetic Methods 1989*; Scheffold, R. Ed.; Springer-Verlag: Berlin, 1989; Vol. 5, p. 115. (b) Narasaka, K. *Synthesis* **1991**, 1. (c) Whitesell, J. K. *Chem. Rev.* **1989**, *89*, 1581.
6. (a) Curran, D. P.; Qi, H. Y.; Geib, S. J.; DeMello, N. C. *J. Am. Chem. Soc.* **1994**, *116*, 3131. (b) Curran, D. P.; DeMello, N. C. *J. Chem. Soc., Chem. Commun.* **1993**, 1314. (c) Qi, H. Ph.D. Thesis University of Pittsburgh, 1995. Barriers are estimated to be <25 kcal/mol.
7. (a) Hughes, A. D.; Price, D. A.; Shishkin, O.; Simpkins, N. S. *Tetrahedron Lett.* **1996**, *37*, 7607. (b) Kitagawa, O.; Izawa, H.; Taguchi, T.; Shiro, M. *Tetrahedron Lett.* **1997**, *38*, 4447. (c) DeMello, N. C. Ph.D. Thesis, University of Pittsburgh, 1995.
8. For a topical overview of these and related types of reactions, see: Clayden, J. *Angew. Chem. Int. Ed. Eng.* **1997**, *36*, 949.
9. Cass, Q. B.; Degani, A. L. G.; Tiritan, M. E.; Matlin, S. A.; Curran, D. P. *Chirality* **1997**, *2*, 9.

10. (a) Stewart, W. E.; Siddall, T. H., III *Chem. Rev.* **1970**, 517. (b) Oki, M. *Top. Stereochem.* Allinger, N. L.; Eliel, E. L.; Wiley, S. **1984**, *14*, 9–19.
11. (a) Pederson, B. F.; Pederson, B. *Tetrahedron Lett.* **1956**, 2995–3001. (b) Kessler, H.; Rieker, A. *Liebigs Ann. Chem.* **1967**, *708*, 57–68. (c) Chupp, J. P.; Olin J. F. *J. Org. Chem.* **1967**, *32*, 2297–2301.
12. (a) Itai, A.; Toriumi, Y.; Saito, S.; Kagechika, H.; Shudo, K. *J. Am. Chem. Soc.* **1992**, *114*, 10649–10650. (b) Azumaya, I.; Yamaguchi, K.; Kagechika, H.; Saito, S.; Itai, A.; Shudo, K. *Yakugaku Zasshi* **1994**, *114*, 414–430. (c) Saito, S.; Toriumi, Y.; Tomioka, N.; Itai, A. *J. Org. Chem.* **1995**, *60*, 4715–4720. (d) Azumaya, I.; Kagechika, H.; Yamaguchi, K.; Shudo, K. *Tetrahedron* **1995**, *51*, 5277–5290. (e) Azumaya, I.; Yamaguchi, K.; Okamoto, I.; Kagechika, H.; Shudo, K. *J. Am. Chem. Soc.* **1995**, *117*, 9083–9084.
13. (a) Oki, M. In *Applications of Dynamic NMR Spectroscopy to Organic Chemistry*, VCH: Deerfield Beach, FL; **1985**, 160–193. (b) Price, B. J.; Eggleston, J. A.; Sutherland, I. O. *J. Chem. Soc. (B)* **1967**, 922–925. (c) Shvo, Y.; Taylor, E. C.; Mislow, K.; Raban, M. *J. Am. Chem. Soc.* **1967**, *89*, 4910–4917. (d) Siddall, T. H., III; Stewart, W. E. *J. Phys. Chem.* **1969**, *73*, 40–45.
14. For representative crystal structures, see: (a) Pederson, B. F. *Acta Chem. Scand.* **1967**, *21*, 1415. (b) Denne, W. A.; Mackay, M. F. *J. Cryst. Mol. Struct.* **1974**, *4*, 141. (c) Boeyens, J. C. A.; Denner, L.; Staskun, S. *S. Afr. J. Chem.* **1987**, *40*, 60. (d) Wang, Q.-P.; Bennet, A. J.; Brown, R. S.; Santarsiero, B. D. *J. Am. Chem. Soc.* **1991**, *113*, 5757. See Ref. 11.
15. Porter, N. A.; Giese, B.; Curran, D. P. *Acc. Chem. Res.* **1991**, *24*, 296–304.
16. The shape of the Z-rotamer is reminiscent of 'sterically protected' esters. See: Suzuki, K.; Seebach, D. *Liebigs Ann. Chem.* **1992**, 51.
17. Curran, D. P.; Heffner, T. A. *J. Org. Chem.* **1990**, *55*, 4585.
18. Reaction of methacrylamide **2e** with *t*-butyl nitrile oxide provided a 1.5/1 mixture of stereoisomers whose relative configurations were not assigned. The major isomer existed in a 1/1 rotamer ratio and the minor isomer existed in a 2.5/1 rotamer ratio.
19. Dewar, M. J. S.; Zoebisch, E. F.; Healy, E. G.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985** *107*, 3902–3909. Calculations were conducted with the MOPAC 93.00 program, J. J. P. Stewart, Fujitsu Limited, Tokyo, Japan (1993). The molecular modelling was performed by the XMol program [Copyright @ 1991, 1992, 1993 by Research Equipment Inc. Minnesota Supercomputer Center, Inc.] Calculations were conducted on IBM Risc 6000 Workstation.
20. Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496–6511.
21. Pirkle, W.; Welch, C. J. *Tetrahedron: Asymmetry* **1994**, *5*, 777.
22. On several occasions, we succeeded in separating diastereomeric *o*-isopropyl benzanilides, only to have them re-equilibrate during the solvent evaporation stage. H. Yamada, unpublished observations.
23. Tiritan, M. E.; Cass, Q. B.; Del Alamo, A.; Matlin, S. A.; Grieb, S. J. *Chirality*, in press.
24. Matlin, S. A.; Tiritan, M. E.; Cass, Q. B.; Boyd, D. R. *Chirality* **1996**. *8*, 147.

(*Received 11 November 1997*)